REMARKS

The Examiner contends that the Information Disclosure Statement filed 10/23/2002 lists a foreign reference number different from the reference submitted for document #BH. The document submitted having reference number 99/64850 is actually **WO 99/64580,** entitled "Microneedle Devices and Methods of Manufacture and Use Thereof". A courtesy copy of the document is provided for the Examiner's convenience (Exhibit A). Additionally, the Examiner contends that not all of the references listed on the information disclosure statement filed January 18, 2005 have been located in the parent application. In order to expedite prosecution, Applicants are submitting herewith a copy of the Information Disclosure Statement, along with copies of references, as filed on January 18, 2005.

Claims 69 and 85 have been amended pursuant to the Examiner's objection to correct the informalities. Claims 69-70, 80, and 85 have been amended to more particularly point out and distinctly claim the subject matter which Applicants regard as their invention.

After entry of this amendment claims 69-75, 77-95 and 97-104 will be pending in the application.

1. THE CLAIMED INVENTION

The claimed invention relates to delivery of substances, including therapeutic (*e.g.*, drugs) and diagnostic substances, to the intradermal compartment of human skin to achieve systemic distribution of that substance in the human body such that the dosage of the substance for achieving the desired biological effect is reduced compared to when the substance is delivered to the subcutaneous compartment. By way of background, human skin is composed of two major tissue layers, an outer epidermis, and an underlying dermis. The epidermis of human skin is made up of five layers (the outermost impermeable barrier is called the stratum corneum) and has a total thickness of about 75 μm to 150 μm. The dermis lies beneath the epidermis, beginning at a depth of about 60 μm - 120 μm below the skin surface, and is approximately 1-2 mm thick. The dermis contains two layers — the uppermost portion contains a bed of capillary and lymphatic vessels. The lower layer is relatively avascular, composed of dense connective tissue. Beneath the epidermis and dermis

is the subcutaneous tissue, composed of connective tissue and fatty tissue. Muscle tissue lies beneath the subcutaneous tissue.

Systemic distribution of drugs is best achieved by direct injection into a vein, *i.e.*, intravenous (IV) administration. However, IV injections are often impractical, requiring trained health care specialists for administration. As a result, intramuscular (IM) and subcutaneous (SC) injections (*i.e.*, injections *below* the skin) are the most commonly used routes of administration, even though these modes of administration result in a different pharmacokinetic profile and lower bioavailability (*i.e.*, lower plasma concentration of drug).

The present invention relates to delivering substances to the intradermal compartment of human skin to achieve systemic distribution of the substance in the human body. The space in the intradermal compartment that is targeted in accordance with the invention is close to the capillary bed, allowing for absorption and systemic distribution of the substance, but is above the peripheral nerve net, thereby eliminating or reducing injection pain. The inventors have unexpectedly found that delivery of substances, drugs, for example, to the intradermal compartment results in systemic distribution with a much improved bioavailability; *e.g.*, a higher plasma level of circulating drug is achieved in a shorter time period (*see* instant specification at Examples 1, Figure 1). The direct benefit is that intradermal administration with enhanced bioavailability allows equivalent biological effect while using less active agent. For example, the dosage of substance administered by intradermal administration can be reduced by at least 10% compared to when the substance is delivered to a subcutaneous compartment of the human subject's skin. This results in overall reduced dosing of the drug providing therapeutic (*e.g.*, reduced side effects) as well as economic benefits over conventional modes of delivery including subcutaneous delivery (See Example VI, Example VIII).

2. THE CLAIMED INVENTION IS NOT OBVIOUS OVER U.S. Patent No. 5,527,288 ("Gross '288") IN VIEW OF U.S. Patent No. 6,007,821 ("Srivastava")

Claims 69-72, 74-75, 77-89, 94-95 and 97-104 stand rejected under 35 U.S.C. §103(a) as unpatentable over U.S. Patent No. 5,527,288 to Gross et al. ("Gross '288") in view of U.S. Patent No. 6,007,821 ("Srivastava"). Applicants respectfully disagree with the rejection because there is no suggestion, either in the references cited by the Examiner or in the knowledge of one of ordinary skill in the art to modify the references or to combine the teachings of the references to arrive at the presently claimed invention.

a. *The Legal Standard*

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation either in the prior art references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. M.P.E.P. 2143.

Prior art references may be combined to render an invention obvious under 35 U.S.C. § 103, however, the teachings of references can be combined only if there is some suggestion or incentive to do so. *ACS Hospital Systems, Inc. v. Montefiore Hospital*, 732 F.2d 1572, 1575 (Fed. Cir. 1984). The teaching or motivation to combine prior art references must be "clear and particular. Broad conclusory statements regarding the teaching of multiple references, standing alone, are not evidence." *In re Dembiczak*, 173 F.3d 994, 999 (Fed. Cir. 1999).

The Federal Circuit has expressly indicated that a *prima facie* case of obviousness requires "objective evidence of record" demonstrating that there is prior art that teaches or suggests combining the asserted references as proposed. *In re Lee*, 277 F.3d 1338, 1341 (Fed. Cir. 2002). More specifically, the motivation to combine references originate from one of three sources: the nature of the problem to be solved, the teachings of the prior art, or the knowledge of persons of ordinary skill in the art. *In re Rouffet*, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998). Consequently, the reason or suggestion in the art for carrying out the invention, must originate from a source other than the knowledge learned from the Applicant's disclosure (*In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988)), and care must be exercised not to use the Applicant's disclosure to fill in the gaps in the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991); *In re Grabiak*, 769 F.2d 729 (Fed. Cir. 1985).

b. *No Suggestion or Motivation to Combine Gross '288 And Srivastava*

The Examiner relies on Srivastava for the teaching that intradermal injections require a lower dosage than do subcutaneous injections and are therefore desirable in view of the associated reduced material cost. The Examiner posits that it would have been obvious to use

the disclosure of Gross '288 to administer the composition using the dosages disclosed by Srivastava. The motivation for the combination, according to the Examiner, would be to use the device of Gross '288 for its intended use.

Applicants respectfully disagree, and respectfully submit that the rejection should be withdrawn because Gross and Srivastava do not make a *prima facia* case of obviousness against the presently pending claims because there was no motivation for the ordinarily skilled artisan to combine these references.

Neither Gross '288 nor Srivastava provide a motivation to combine their teachings. As discussed above, obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is a suggestion found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *MPEP § 2143.01.*

Gross '288 relates to devices for allegedly delivering a drug into the intradermal compartment of the subject's skin. However, even by Gross' own admission its "intradermal devices" do not specifically target the intradermal space but rather haphazardly or non-selectively administers the drug "below the epidermis, *i.e.*, to the interface between the epdiermis and the dermis or to the interior of the dermis or subcutaneously (*see*, Gross '288 at col. 3, *ll.* 46-49). Gross '288 consistently characterizes the needles used in these devices as being of just sufficient length to penetrate through the epidermis." (*see*, Gross '288 at col. 7, *ll.* 54-55, emphasis added.). Gross' 288 does not teach or suggest using its purported intradermal devices to reduce the dosage of the drug administered which would be preferred economically, and in fact is silent on the required dosages of the drugs.

Srivastava relates to immunotherapeutic methods for administering heat shock protein (hsp)-containing compositions (*i.e.*, immunogenic compositions) for the treatment of autoimmune diseases, *e.g.*, insulin-dependent diabetes mellitus. Srivastava is concerned with suppression of immune response via the hsps which exert a local and transforming effect at the site of autoimmune cellular activity (*see*, col. 4, *ll.* 31-33). Srivastava's methods for treating an autoimmune disease in a subject are based on hsp immunotherapeutic agents which mediate a *local, cellular response*, rather than achieve a systemic effect (*see*, col. 5, *l.* 62 to col. 6, *l.* 13). Srivastava is solely concerned with providing a local, cellular effect of an immunotherapeutic agent and provides no suggestion or motivation to reduce the dosage of a

substance, *e.g.*, drug, for ***systemic distribution*** by delivering a substance, *e.g.*, drug, into the intradermal space as opposed to the subcutaneous compartment of skin.

Gross '288 relates to delivery of a liquid drug (intended for systemic distribution) purportedly to the intradermal compartment. On the other hand Srivastava is concerned with delivering immunogenic compositions for achieving a cellular local effect -- not a systemic distribution. Thus, skilled artisans concerned with increasing a drug's bioavailability, and thereby decreasing the systemically-administered dose needed to achieve a desired drug-effect, would not apply or combine the disclosure in Srivastava with those in Gross. Moreover, the references must be viewed without the benefit of hindsight vision afforded by Applicants' claimed invention. *M.P.E.P. § 2141.* Absent a suggestion for the teaching that a lower dose can be administered by intradermal injection than by subcutaneous injection to achieve the same therapeutic effect, the rejection cannot stand.

Accordingly, in view of the amendments to the claims and the arguments presented above, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

c. ***Gross '288 and Srivastava fail to provide a reasonable expectation of success***

As mentioned above, a prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success. *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Both the suggestion and the reasonable expectation of success must be found in the prior art and not in the Applicants' disclosure. *In re Vaeck* 947 F.2d 488 (Fed. Cir. 1991); *In re O'Farrell*, 853 F.2d 894, 7 USPQ2d 1673.

In this case, neither Gross nor Srivastava provide a reasonable expectation of success. There is no disclosure or evidence in either reference that would reasonably suggest that the claimed invention would be successful. Both references are devoid of any teaching regarding reducing the dosage of the substance delivered using its purported intradermal devices for achieving a systemic distribution. Gross does not even provide an invitation for such experimentation and thus fails to provide a reasonable expectation of success for achieving the claimed invention, *i.e.*, delivering a drug into the intradermal compartment wherein the dose for achieving systemic distribution is reduced by at least 10% as compared to

subcutaneous delivery. In fact it is unpredictable based on Gross' own disclosure when Gross' devices would deposit the substance into the intradermal compartment as opposed to other skin layers. Thus Gross's disclosure could not proffer a reasonable expectation of success for reducing dosage of the substance when delivered to the intradermal space. As such, Applicants assert that this prong of the standard for obviousness rejection is unmet.

d. ***Gross 288 and Srivastava fail to teach or suggest all the claim limitations***

The Examiner contends that Gross '288 meets most of the claimed limitations (*i.e.*, needle length, site of placement and outlet opening size) but concedes that the reference fails to disclose a reduced intradermal dosage of the substance for achieving a biological effect in comparison to subcutaneous administration. Applicants respectfully disagree, and respectfully submit the rejection should be withdrawn because Gross '288 and Srivastava fail to teach all of Applicants' claimed features, especially in view of the current claim amendments.

Here, Gross '288 and Srivastava fail to teach the exposed height of the needle outlet as required in claims 69- 84. Gross '288 and Srivastava also fail to teach microneedles having a length sufficient to penetrate the intradermal compartment and an outlet at a depth within the intradermal compartment as required in claims 85-104. Finally, Gross '288 and Srivastava also fail to teach intradermal administration whereby the dosage of the substance for achieving a systemic distribution is reduced by at least 10% as compared to subcutaenous administration. In order to establish a *prima facie* case of obviousness the prior art references must teach or suggest all of the claim limitations. *M.P.E.P. §2142.* Consequently, Applicants submit that the rejection is misplaced.

(i) Examiner's Reliance on Figure 3 of Gross '288 is Erroneous Pursuant to M.P.E.P. § 2125

The Examiner asserts that Gross '288 discloses an intradermal drug delivery device that includes administering a substance through a small gauge needle. Furthermore, the Examiner contends that Gross '288 discloses that the device has a needle with an outlet opening at a depth of 0.3 to 1.0 mm when inserted into the dermis. According to the Examiner, the device would deliver the substance at a depth between 0.3 to 2 mm.

The Examiner fails to find express support for the dimension of the needle outlet as required by Applicants' claims. Instead, the Examiner erroneously infers an outlet opening

of about 0.1 to 1.0 mm by citing the illustration of the device in Figure 3 of Gross '288. Merely relying on the Figure, the Examiner estimates that since the diameter of the outlet opening is "about 1/3 the length of the needle", the outlet opening is 0.1 to 1.0 mm based on a needle length of 0.3 to 3 mm.

Applicants respectfully disagree with the Examiner. The Examiner has improperly relied on the illustration of the needle in Figure 3 of Gross '288 to infer the dimension of the needle outlet as set forth in Applicants' claims. When a reference fails to specify that the drawings are to scale, arguments supported by measurement of the drawing features are *not* evidence of actual proportions. *M.P.E.P. § 2125.* Here, the Examiner has improperly inferred a needle opening of 0.1 to 1 mm based on a comparison of the needle length and outlet in the illustration of the needle in Figure 3. The reference, however, is silent in disclosing whether the illustrations are drawn to scale. Moreover, the reference is silent as to any description of the needle outlet in Figure 3. Accordingly, the Examiner has failed to establish that Gross '288 provides a description of a needle with the dimensions required by the claimed invention..

2. THE CLAIMED INVENTION IS NOT OBVIOUS OVER U.S. Patent No. 5,800,420 ("Gross '420") IN VIEW OF U.S. Patent No. 6,007,821 ("Srivastava")

Claims 69, 73, 85 and 93 stand rejected under 35 U.S.C. §103(a) as unpatentable over U.S. Patent No. 5,800,420 (Gross '420) in view of U.S. Patent No. 6,007,821 (Srivastava). The Examiner asserts that Gross '420 teaches an intradermal compartment drug delivery device that can deliver a substance through a small gauge hollow needle. The Examiner alleges that the reference discloses that the needle has an exposed height of 0.3 to 1.0 mm which the Examiner reasons would result in the delivery of the substance at a depth of between 0.3 to 2 mm. Furthermore, the Examiner suggests that the disclosure of the device's ability to deliver a bolus injection inherently discloses an administration having less than 10 minutes duration. Finally, the Examiner posits that the device in Gross'420 communicates with the capillary-containing tissue and infers that this tissue is the same as the intradermal compartment.

In addition, the Examiner contends that Gross '420 meets most of the claimed limitations (*i.e.*, depth of delivery, needle, exposed height of outlet) but concedes that the reference fails to disclose a reduced intradermal dosage of the substance for achieving a

biological effect in comparison to subcutaneous administration. The Examiner relies on Srivastava for the teaching that intradermal injections require a lower dosage than do subcutaneous injections, and are therefore desirable in view of the associated reduced material cost. The Examiner posits that it would have been obvious to use the disclosure of Gross '420 to administer the composition using the dosages disclosed by Srivastava. The motivation for the combination, according to the Examiner, would be to use the device of Gross '420 for its intended use.

Applicants respectfully disagree.

First, with respect to claims 69 and 73, Gross '420 fails to disclose the exposed height of the needle outlet as described in Applicants' claims. A careful reading of the specific passage cited by the Examiner (*see*, Gross '420 col. 10, *ll.* 32-39) that the passage fails to specifically note the needle outlet height, in contrast to the other discussed needle features (*e.g.*, height of needle projection, outer and inner needle diameter). Consequently, the cited references fail to teach all of Applicants' claimed features.

Second, in applying the rejection to claims 69, 73, 85 and 93, contrary to the Examiner's contention, Srivastava fails to suggest a motivation to modify the disclosure of Gross '420. As discussed *supra*, Srivastava relates to immunotherapeutic methods for administering heat shock protein (hsp)-containing compositions (*i.e.*, immunogenic compositions) for the treatment of autoimmune diseases, *e.g.*, insulin-dependent diabetes mellitus, while Gross '288 relates to delivery of a liquid drug (intended for systemic distribution) purportedly to the intradermal compartment. Skilled artisans, concerned with increasing a drug's bioavailability, and thereby decreasing the systemically-administered dose needed to achieve a desired drug-effect, would not likely rely on a reference such as Srivastava that delivers immunogenic compositions intended for exerting a local effect. Moreover, the references must be viewed without the benefit of hindsight vision afforded by Applicants' claimed invention. *MPEP § 2141.* Absent a suggestion for the teaching that a lower dose can be administered by intradermal injection than by subcutaneous injection to achieve the same therapeutic effect, the rejection cannot stand.

Accordingly, in view of the amendments to the claims and the arguments presented above, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

3. THE CLAIMED INVENTION IS NOT OBVIOUS OVER U.S. Patent No. 5,527,288 ("Gross '288") and U.S. Patent No. 5,800,420 (Gross '420) IN VIEW OF U.S. Patent No. 6,007,821 ("Srivastava") AND FURTHER IN VIEW OF U.S. Patent No. 6,537,242 ("Palmer")

Claims 90-92 stand rejected under 35 U.S.C. §103(a) as unpatentable over U.S. Patent No. 5,527,288 (Gross '288) and U.S. Patent No. 5,800,420 (Gross '420) in view of U.S. Patent No. 6,007,821 (Srivastava) in further view of U.S. Patent No. 6,537,242 ("Palmer"). The Examiner contends that Palmer discloses an intradermal drug delivery device that includes an array of microneedles.

Without conceding the correctness of the merits of the rejection, Applicants note that Palmer should properly be disqualified as prior art against the claimed invention as the subject matter and the claimed invention were, at the time the invention was made, subject to an obligation of assignment to the same person pursuant to *MPEP § 706.02(l)(1)*.

> Statement Concerning Common Ownership
> U.S. Patent Application Serial No. 10/028,989 ("the '989 application") and U.S. Patent No. 6,537,242, were, at the time the invention of the '989 application was made, owned by Becton Dickinson and Company.

As further objective evidence of common ownership, the reel and frame numbers for the recorded assignment for the '989 application are 012846/0914, and the reel and frame number for the recorded assignment for U.S. Patent No. 6,537,242 are 010870/0277.

Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) are respectfully requested.

CONCLUSION

In light of the above amendments and remarks, the Applicants respectfully request that the Examiner enter the amendments and consider the remarks made herein. Withdrawal of all rejections, and an early allowance is earnestly sought. The Examiner is invited to call the undersigned attorney if a telephone call could help resolve any remaining items.

Respectfully submitted,

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